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Pharmacokinetics and pharmacodynamics of anti-infective agents during continuous veno-venous hemofiltration in critically ill patients: Lessons learned from an ancillary study of the IVOIRE trial

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ABSTRACT

Background: Hemofiltration rate, changes in blood and ultrafiltration flow, and discrepancies between the prescribed and administered doses strongly influence pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents during continuous veno-venous hemofiltration (CVVH) in critically ill patients. **Methods**: Ancillary data were from the prospective multicenter IVOIRE (hIgh VOlume in Intensive caRE) study. High volume (HV, 70 mL/kg/h) was at random compared with standard volume (SV, 35 mL/kg/h) CVVH in septic shock patients with acute kidney injury (AKI). PK/PD parameters for all antimicrobial agents used in each patient were studied during five days. **Results**: Antimicrobial treatment met efficacy targets for both percentage of time above the minimal inhibitory concentration and inhibitory quotient. A significant correlation was observed between the ultrafiltration flow and total systemic clearance (Spearman test: $P < 0.005$) and between CVVH clearance and drug elimination half-life (Spearman test: $P < 0.005$). All agents were easily filtered. Mean sieving coefficient ranged from 38.7% to 96.7%. Mean elimination half-life of all agents was significantly shorter during HV-CVVH (from 1.29 to 28.54 h) than during SV-CVVH (from 1.51 to 33.85 h) ($P < 0.05$). **Conclusions**:This study confirms that CVVH influences the PK/PD behavior of most antimicrobial agents. Antimicrobial elimination was directly correlated with convection rate. Current antimicrobial dose recommendations will expose patients to underdosing and increase the risk for treatment failure and development of resistance. Dose recommendations are proposed for some major antibiotic and antifungal treatments in patients receiving at least 25 mL/kg/h CVVH.

Key words: pharmacokinetics, pharmacodynamics, continuous veno-venous hemofiltration, high volume hemofiltration, septic shock, antibiotics, antibiotic dosage

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INTRODUCTION

Adequate antimicrobial therapy is essential to maximize the survival of critically ill patients.[1] Anti-infective drugs are classified as time-dependent (*e.g.*, β-lactams, carbapenems, macrolides, fluconazole, vancomycin) when their bactericidal effect depends on the time that plasma levels remain above a threshold minimal inhibitory concentration (MIC), or concentration-dependent (*e.g.*, aminoglycosides, fluoroquinolones, echinocandins, daptomycin, polyenes, doxycyclin) when the height of peak concentration above the MIC determines the killing effect.[2] Acute kidney injury (AKI) significantly interferes with the administration of anti-infective agents. Antibacterial pharmacokinetics (PK) are affected by AKI itself, the underlying or accompanying disease process, and the applied renal replacement therapy. Continuous renal replacement therapy (CRRT) causes alterations in drug clearance. Factors influencing PK and pharmacodynamics (PD) of antimicrobial drugs during CRRT include the CRRT mode (diffusion, convection, or both), changes in blood and ultrafiltration flow, type of filtration membrane (*e.g.*, highly adsorptive filters), and discrepancies between prescribed and actually administered antimicrobial dose. For these reasons, drug dose adjustment in critically ill patients receiving CRRT is challenging.[3,4,5]

Continuous veno-venous hemofiltration (CVVH) is the most commonly used CRRT technique in the critical care setting.[5] Antimicrobial drug behavior during CVVH is still scarcely documented. This is of concern because higher ultrafiltrate doses are increasingly promoted.[7,8,9]. Moreover, great divergence exist between predicted and observed removal of antibiotics in critically ill CVVH-treated patients.[10]

We applied the established PK/PD principles in a subgroup of patients from the previously published IVOIRE trial, which compared high volume (HV; 70 mL/kg/h) with standard volume (SV; 35 mL/kg/h) CVVH in septic shock patients with AKI.[11] Importantly, the IVOIRE trial was conceived in 2004 when PK/PD knowledge was still in its infancy. At that time, no consensus existed regarding antimicrobial dosing during HV-CVVH. Also, the primary endpoint of the IVOIRE study was comparing the 28-day mortality between the patients treated with HV-CVVH and SV-CVVH. Therefore, upfront use of higher antimicrobial doses in the HV-CVVH group was not supported because it was thought to produce substantial outcome bias. It was decided to administer all drugs according to the accepted dose recommendations at that time (*i.e.*, weight-adapted, as in patients without AKI) and to treat both SV-CVVH and HV-CVVH patients with comparable doses of antimicrobials either in continuous or intermittent infusion.

The current study is aimed to assess whether a different convection rate determines antimicrobial PK behavior during CVVH. The study results also allowed to create dose recommendations for some of the most commonly used antimicrobials in critically ill patients receiving a CVVH dose of at least 25 mL/kg/h.

PATIENTS AND METHODS

Patients

PK/PD parameters of all administered antimicrobial agents were evaluated in a subgroup of patients who completed a 96 h therapy within the scope of the IVOIRE study. All observations were made abiding the standard routine patient care incorporated within the IVOIRE study protocol.[11] The Institutional Ethical Committee waived a formal approval procedure.

Hemofiltration Technique

A 14F coaxial double lumen hemofiltration catheter was inserted either in the right internal jugular vein or in the femoral veins. CVVH was performed using an Aquarius® hemofiltration circuit (Edwards Life Sciences), with a 1.9 m^2 Aquamax® polyethersulfone filter (Edwards Life Sciences). Since this filter is non-adsorptive, antibiotic elimination is determined by ultrafiltration alone. Hemofiltration treatment was initiated according to randomization towards either SV-CVVH or HV-CVVH. Blood flow rate was adapted to obtain a filtration fraction ≤ 25%. Anticoagulation was ensured by non-fractionated heparin. Filters were changed every 48 h or in case of early clotting. Substitution was divided in a 1/3–2/3 proportion between pre- and post-dilution. Patients who still required CVVH at the end of the study were continued on standard hemofiltration at 35 mL/kg/h.

Sample collection

Mass-transfer concept was used to evaluate the concentration of cleared and absorbed antimicrobials. Indicative samples were taken after 12 or 24 h PK steady-state. Five samples were collected in both groups (at H1 [*i.e.*, 1 h after antimicrobial infusion], H3, H6, H9 and at H12 or H24). Three samples were taken for each time period, one from the venous line after the filter, one from the effluent bag and one from the patient's arterial catheter. As predilution was used, sampling before the filter was not applied. Time and total effluent volume in the bags were recorded for each sample. All plasma and ultrafiltrate samples were placed in 5 ml Vacutainer tubes and immediately centrifuged and frozen at -80°C until assayed.

Sample assays

Plasma and ultrafiltrate concentrations of anti-infective agents were determined with reversed-phase high-performance liquid chromatography (HPLC) using an

Table 1: Demographic characteristics

Demographic data	All	HV	LV
Age (years)	66 ± 12	69 ± 9	63 ± 14
Height (cm)	169 ± 10	170 ± 8	167 ± 12
Weight (kg)	75 ± 18	77 ± 22	73 ± 13
Gender (M/F)	28/14	15/7	13/7
SAPS 2	63 ± 10	65 ± 8	61 ± 12
SOFA	12 ± 2	12 ± 2	12 ± 2
Protein	45 ± 8	45 ± 8	46 ± 9
Albumin	21 ± 4	21 ± 4	22 ± 3
Creatinine	243 ± 116	278 ± 128	196 ± 82
Pathology	42	22	20
Peritonitis	26	15	11
Sepsis	3	1	2
Mediastinitis	4	2	2
Pneumonia	4	1	3
Endocarditis	5	3	2
Urine output (24 h)	223 ± 167	195 ± 166	253 ± 167
Blood flow rate (mL/min)	278 ± 51	317 ± 37	234 ± 18
Ultrafiltration rate (mL/h)	3956 ± 1602	5221 ± 1137	2557 ± 433
28-day mortality	15	8	7

HV: High volume; LV: Low volume.

adapted ultraviolet (UV) detection method.[13–15] Plasma samples were extracted by **SPE**? with Phenomenex Strata-X™ or Varian Plexa™ cartridges (for azoles) or ultra-filtered with Microcon™ devices. Dialysate/ultrafiltrate samples underwent no extraction but were directly injected into the system. Chromatographic separation was performed on Prontosil AQ+ 150 x 4.6 mm 5 μm columns (Bischoff), or on a Gemini C6-phenyl 150 x 4.6 mm 5 μm column (Phenomenex) for azoles. Mobile phases used phosphate buffers (at pH between 3.5 and 7) and acetonitrile. TEA 0.04% at pH 2.7 replaced phosphate buffer for piperacilline/tazobactam and ofloxacin. Wavelengths between 210 and 320 nm were used for UV detection. All HPLC methods were validated according to bioanalytical FDA criteria.[16] Linezolid, imipenem, and ertapenem were used as an internal standard. Coefficients of determination (r^2) for the plasma assays over the standard curves concentration ranges were all above 0.99 with intercept close to zero for all studies. Within- and between-day coefficients of variation (CV) for plasma samples ranged respectively from 0.84% to 2.52% and from 1.36% to 5.43% at the chosen quality control concentrations. Coefficients of variation (r^2) for the ultrafiltrate assays over the standard curves concentration ranges were all above 0.99 and intercept close to zero for all studies. Here, within- and between-day CV for ultrafiltrate samples ranged respectively from 0.78% to 2.43% and from 1.08% to 4.86% at the chosen quality control concentrations. Within- and between-day accuracy for the plasma and ultrafiltrate assays ranged respectively from 96.23% to 104.32% and from 98.24% to 102.68%. All assays had good sensitivity. *Limit of detection (*LOD) and limit of quantification (LOQ) were under minimal concentrations measured on patients. All HPLC assay parameters are summarized in Table 2.

Pharmacokinetic analysis

Plasma concentration-time data for all anti-infective agents were analyzed by standard PK methods using Kinetica™ software and an open one-compartmental model with first order elimination (Kinetica™ version 4.4 for Windows, San Diego, CA). Pre-membrane plasma drug concentrations were used to determine the PK parameters. The apparent terminal elimination rate constant (k_{el}) was assessed by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. Maximum plasma drug concentration (C_{max}) was obtained at the end of the drug infusion. Minimum plasma concentration (C_{min}) was determined by direct measurement at the end of the dosing interval. Steady-state concentration (C_{ss}) was determined at PK steady-state during continuous infusion. The area

Table 2: HPLC assays parameters.

	Column	Mobile phase	λ (nm)	Plasma extraction	LOD (µg/mL)	LOQ (µg/mL)	Volume injected (µL)
Ertapenem	Prontosil AQ+	Na_2HPO_4 pH = 6.5/ACN v/v	305	Ultrafiltration Microcon YM10™	0.05	0.25	40
Imipenem	Prontosil AQ+	Na_2HPO_4 pH = 6.5/ACN v/v	305	Ultrafiltration Microcon YM10™	0.04	0.20	40
Doripenem	Prontosil AQ+	Na_2HPO_4 pH = 6.5/ACN v/v	305	Ultrafiltration Microcon YM10™	0.05	0.25	40
Ceftriaxone	Prontosil AQ+	Na_2HPO_4 pH = 7/ACN v/v	272	SPE Strata-X™	0.05	0.25	20
Piperacilline /Tazobactam	Prontosil AQ+	TEA 0,04% pH = 2.7/ACN v/v	210	SPE Strata-X™	0.15	0.50	10
Ofloxacine	Prontosil AQ+	TEA 0,04% pH = 2.7/ACN v/v	295	SPE Strata-X™	0.03	0.15	20
Linezolid	Prontosil AQ+	KH_2PO_4 pH = 3.5/ACN v/v	255	SPE Strata-X™	0.25	0.75	20
Daptomycine	Prontosil AQ+	Na_2HPO_4 pH = 5.5/ACN v/v	210	SPE Strata-X™	0.15	0.50	20
Metronidazole	Prontosil AQ+	Na_2HPO_4 pH = 7/ACN v/v	320	SPE Strata-X™	0.04	0.20	20
Fluconazole	Gemini C6-phenyl	Na_2HPO_4 pH = 7/ACN v/v	260	SPE Varian Plexa™	0.02	0.05	25
Voriconazole	Gemini C6-phenyl	Na_2HPO_4 pH = 7/ACN v/v	260	SPE Varian Plexa™	0.02	0.05	25

SPE: Solid phase extraction; ACN: acetonitrile; λ = wavelength; LOD: limit of detection; LOQ: limit of quantification.

under the concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$) was calculated by the linear trapezoidal summation method. Since true PK steady-state conditions could not be assumed in all patients, volume of distribution (V_d) was calculated by non-steady-state methods, which take into account the number of doses previously administered. Total systemic clearance (CL_S) was calculated by dose/$AUC_{0-\tau}$. During CVVH, drugs are predominantly cleared by convection but also in part by membrane adsorption. The sieving coefficient (Sc), the drug concentration in ultrafiltrate, was calculated as $2 \times C_{uf}/(C_a + C_v)$, where C_{uf} is the drug concentration in ultrafiltrate, C_a – the drug concentration in pre-membrane plasma (*i.e.*, plasma obtained from the arterial line in predilution), and C_v – the drug concentration in post-membrane plasma. Clearance of drug across the membrane during CVVH (CL_{CVVH}) was calculated by $C_S \times Q_{uf}$ x dilution factor (dilution factor = blood flow (Qb) / (Qb + predilution flow (Qs pre) with Qs pre = volume infused in predilution). The percentage of CL_S attributed to CL_{CVVH} (%CL_S) is calculated as (CL_{CVVH}/CL_S) × 100. Non-renal clearance (CL_{NR}), which is mainly the residual renal and hepatic clearance, was calculated as CL_S - CL_{CVVH} as urine output in the study population was negligible. All calculations were made by programming PK and CVVH clearance equations into Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) spreadsheets. Using Excel, measures of central tendency and variability were evaluated for all patient and CVVH characteristics, PK parameters, and CVVH clearance. European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to define micro-organism resistance.

PK/PD analysis

General PK/PD principles were considered and their clinical application and dosing implications for critically ill patients addressed. The time during which plasma concentrations of free drug are above the minimal inhibitory concentration (MIC) of the infecting pathogen (T > MIC) was then calculated as natural log (maximum bacterial population size. (Cfu_{max}) /C_{MIC})/k_{el}, where C_{MIC} is the MIC for the organism. The percent T% > MIC was determined by (T > MIC/τ) × 100, where τ is the dosing interval. Target goal for T% > MIC was > 40 to 50% for

clinical efficacy and prevention of resistance. The inhibitory quotient (IQ) corresponding to the C_{max}/MIC ratio and the inhibitory area under the curve (AUIC) corresponding to the AUC/MIC ratio were calculated. Target goals for IQ and AUIC were > 4 and > 125 respectively for clinical efficacy and prevention of resistance especially for Gram-negative organisms and for concentration-dependent antibiotics. MICs of antibiotics for isolated pathogens were determined by the local clinical microbiology laboratory. Predicted *T*% > MIC for dosing regimens not observed in the study patients were calculated based on PK parameters derived from the individual patients within both CVVH groups.

Statistical analysis

Differences between demographic variables among patients receiving either HV- or SV-CVVH were assessed by one-way analysis of variance fixed-effects model for continuous variables or by two-way chi-square test for categorical variables. Differences among calculated PK parameters were assessed by the two-tailed Mann-Whitney rank sum test for unpaired non-parametric data. Correlations between PK variables were determined using the Spearman's rank correlation coefficient for non-parametric data. All statistical tests were performed with the Statistica™ version 6.1 for Windows (Statistica™ Software, San Diego, CA). *P* values ≤ 0.05 were considered to be significant.

RESULTS

Forty-five patients were studied for four consecutive days. During this study period, 5 patients received one, 34 patients received two, and 6 patients received three antimicrobial agents. Characteristics of the patients are shown in Table 1. Two patients died in the first few hours of treatment and the samples of one patient were damaged during transportation. Thus, 42 patients were evaluable. Mean arterial plasma and effluent concentrations of the anti-infective agents in both CVVH groups are illustrated in Figure 1. The PK parameters are presented in Tables 3 and 3 bis. All agents were easily filtered. Mean Sc ranged from 38.70% to 96.70%. Mean t1/2 of all agents during HV-CVVH (from 1.29 to 28.54 h) was significantly shorter than during SV CVVH (from 1.51 to 33.85 h) ($P < 0.05$). CLs, CL_{CVVH}, and CL_{NR} of all agents were significantly higher during HV-CVVH than during SV-CVVH ($P < 0.05$). Renal excretion of all agents ranged between 13% and 100% and 9% and 57% for respectively HV- and SV-CVVH. Drug removal was moderate with SV-CVVH but became significantly enhanced by HV-CVVH due to increased ultrafiltrate flow. Drug half-live was extended, probably because of a sepsis-induced Vd increase in most patients. Irrespective of the antimicrobial agent, PK parameters were similar to those observed in infected patients without impaired renal function. The PK/PD parameters (Table 4) demonstrated that treatments met efficiency targets for T% > MIC and IQ. Finally, a significant correlation existed between Quf and CL_S (Spearman test: $P < 0.005$) and between CL_{CVVH} and elimination half-life (Spearman test: $P < 0.005$).

DISCUSSION

Antimicrobial clearance during CRRT is determined by several chemical drug characteristics.[17] Molecular weight and drug solubility are no limiting factors since antimicrobials are mostly small hydrophilic molecules.[18,19] Drug Vd may increase significantly during resuscitation of septic shock. Thus, extracellular water and by extension current body weight must be considered to optimize the dose of certain antibiotic classes (*e.g.*, aminoglycosides).[20] Protein binding remains the most important factor limiting antimicrobial elimination by convective CRRT.[21] Protein-bound molecules do not pass the pores of the currently used dialysis membranes. However, protein binding in critically ill patients may be highly variable. An increase in unbound drug will increase Sc and Sd, and hence, clearance by CRRT.[22] Based on the aforementioned, antimicrobial drugs can be categorized as "highly", "moderately" or "not at all" eliminated by CRRT.

Antimicrobial agents have three "killing profiles": time-dependent, concentration-dependent, or a combination of both. These profiles determine the drug dosing to obtain maximum therapeutic efficacy at minimal risk for the development of resistance and toxicity.[23] CL_{NR} was significantly higher for all agents during HV-CVVH as compared with SV-CVVH, which is somewhat unexpected because of the augmented CL_{CVVH} in the HV-CVVH group.

Drugs highly influenced by CRRT

Time-dependent killing

The β-lactams (penicillins, cephalosporins, carbapenems and monobactams) are small hydrophilic molecules and thus likely to be significantly cleared by CRRT. They exhibit time-dependent killing and have a slow continuous bactericidal effect. Killing is most related to the time during which serum concentration exceeds 1 to 5 times the MIC and, in part, also to a continued suppression of bacterial growth even when drug concentrations fall below MIC (*i.e.*, the post-antibiotic effect).[24] To obtain maximal bactericidal activity, a T > MIC of 50 to 60% is required for penicillins and monobactams, 60 to 70% for cephalosporins and 40% for carbapenems.

Piperacillin-tazobactam

Mueller *et al.* investigated the PK of piperacillin-tazobactam in anuric patients treated with CVVHD. The elimination

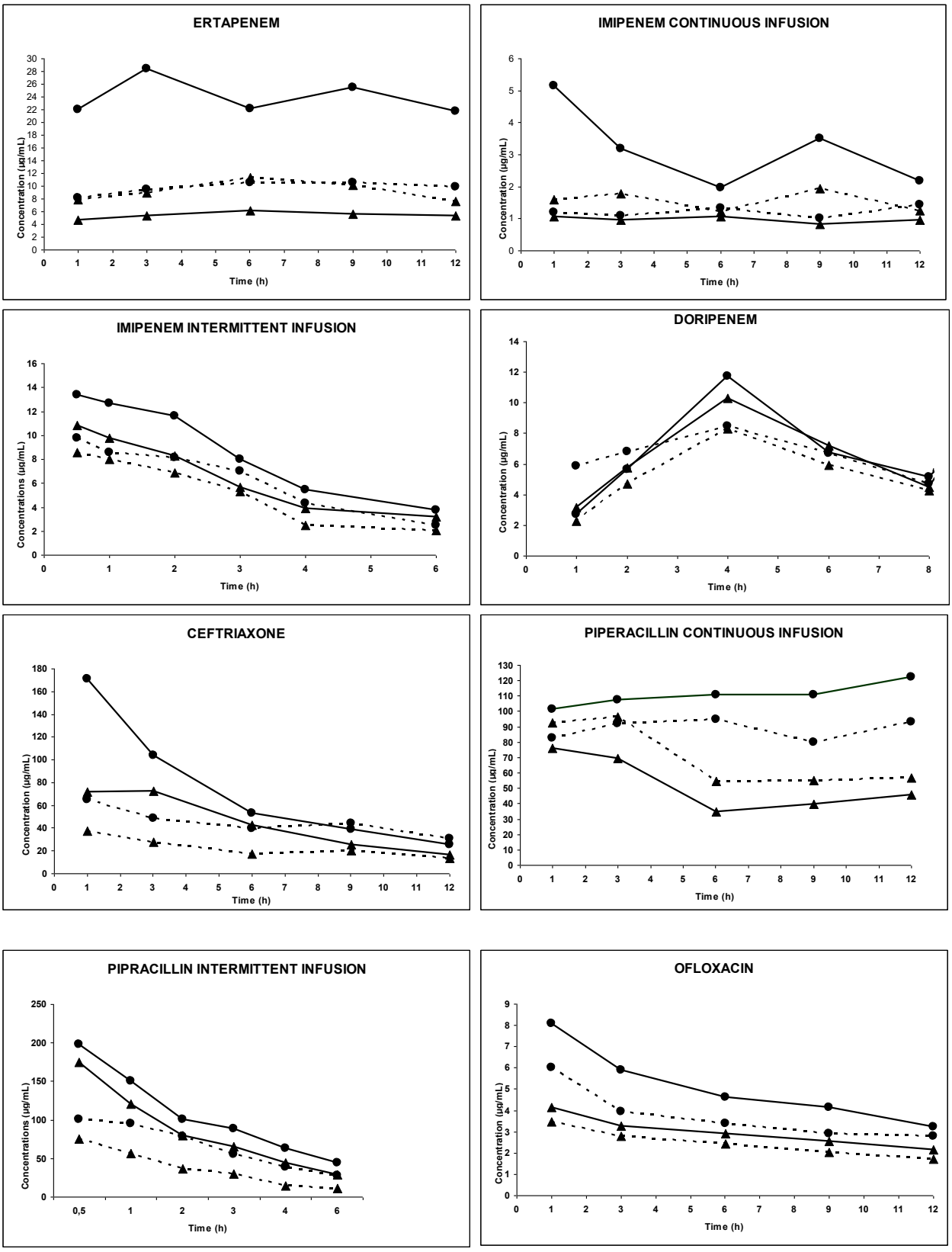
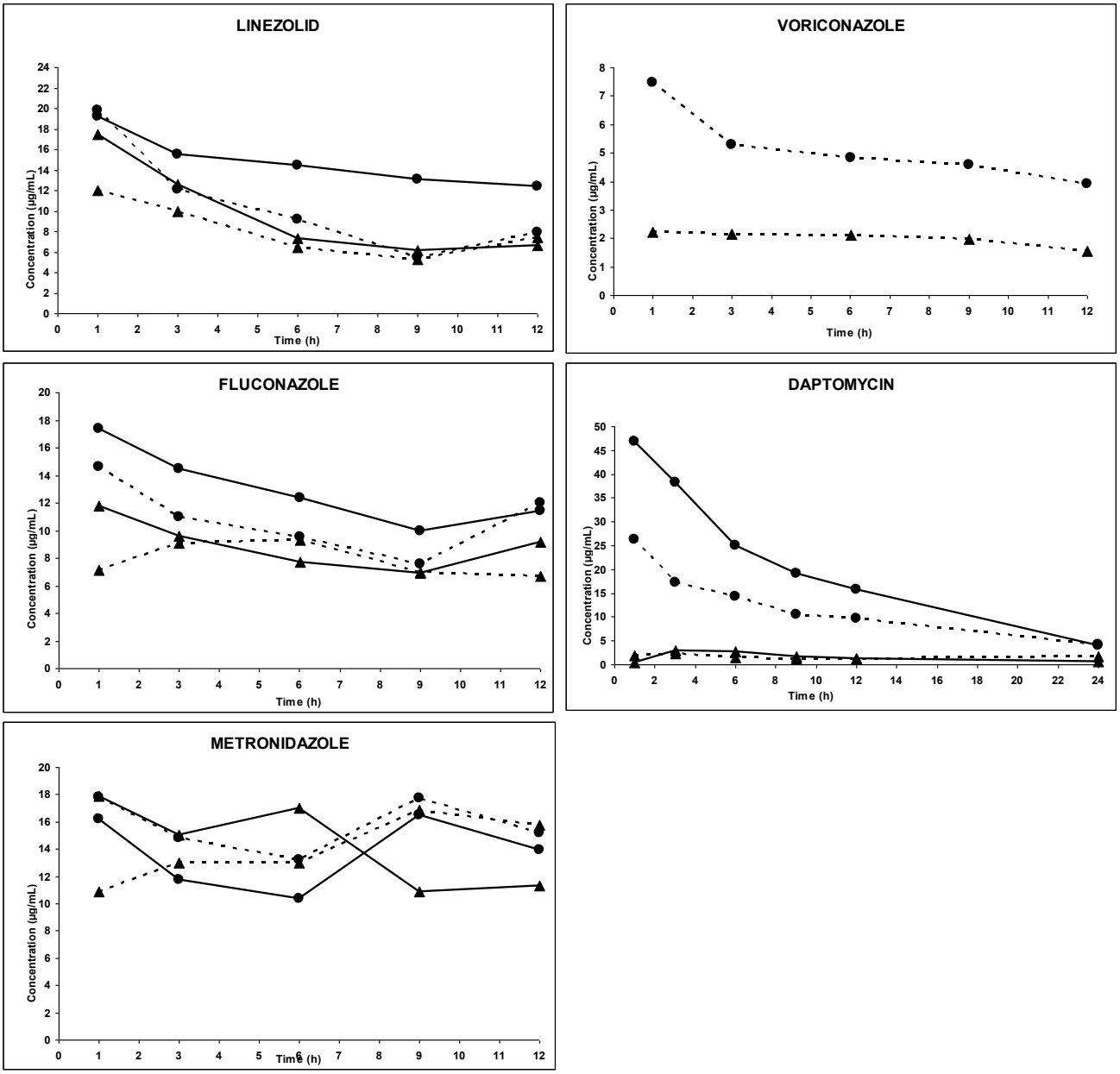


Figure 1: Evolution of arterial plasma concentrations and effluent versus time for anti-infective agents in IVOIRE study during high volume CVVH (HD) and standard volume CVVH (BD)



continued**Figure 1:** Evolution of arterial plasma concentrations and effluent versus time for anti-infective agents in IVOIRE study during high volume CVVH (HD) and standard volume CVVH (BD)

half-life of piperacillin was 4.3 ± 1.2 h, and that of tazobactam 5.6 ± 1.3 h. The contribution of CVVHD to the overall elimination was relevant (> 25%) for both drugs.[25] A recent study in critically ill patients on CVVHDF receiving piperacillin-tazobactam (4 g/0.5 g) every 8 h showed a total clearance of 5.1 (4.2–6.2) L/h and 3.8 (3.3–4.2) L/h and a CVVHDF clearance of 2.5 (2.3–3.1) L/h and 2.5 (2.3–3.2) L/h for piperacillin and tazobactam, respectively.[26] In patients treated with CVVHDF and receiving a 4 h infusion of piperacillin 4 g / tazobactam 0.5 g every 8 h, Awissi *et al.* found a median total clearance of 65.82 mL/min (53.79–102.87), and a median renal clearance of 0.16 mL/min (0.05–3.04). Median CRRT dose was 32.0 mL/kg/h (25.0–39.8).[27] Although some studies suggest a better outcome in critically ill patients receiving prolonged infusion, the level of evidence is moderate.[28] In our study, the *in vivo* concentration obtained after a daily high dose (16 g) continuous but not bolus infusion of piperacillin was adequate, stable throughout time, and within the recommended range for efficacy even in HV-CVVH treated patients. This underscores that piperacillin treatment during CRRT is most efficacious when administered as a loading dose followed by continuous infusion especially at MIC values of 16 to 32 mg/L.[29]

Imipenem

Fish *et al.* studied the PK of imipenem during CVVH and continuous veno-venous hemodiafiltration (CVVHDF). Mean CLs and elimination half-life (t1/2) of imipenem were 145 ± 18 mL/min and 2.7 ± 1.3 h during CVVH and 178 ± 18 mL/min and 2.6 ± 1.6 h during CVVHDF, respectively. Imipenem clearance was substantially increased during both CVVH and CVVHDF, with membrane clearance representing respectively 25% and 32% of CLs.[30] We found mean imipenem SC, CL_{CVVH} and t1/2 ranging from 52.40 to 80.70%, 16.67 to 65.25 mL/min, and 1.29 to 1.51 h respectively. Total clearances were higher than previously published (158.82 to 506.83 mL/min) with membrane clearance ranging from 9% to 18%. [31]

Ertapenem and doripenem

The newer carbapenems ertapenem and doripenem are more stable after reconstitution and have a longer t1/2. Mistry *et al.* showed that hemodialysis cleared approximately 30% of the ertapenem dose.[32] Hidaka *et al.* showed that total body clearance of doripenem was 58.0 ± 12.7 mL/min, including 13.5 ± 1.6 mL/min CVVHDF clearance. Mean t1/2 of doripenem was 7.9 ± 3.7 h. Thus, under the conditions tested, CVVHDF appeared to have little effect on doripenem clearance. Therefore, serum levels of doripenem during CVVHDF can be controlled by adjustment of dose and dosing interval in accordance with residual renal function.[33] Cirillo *et al.* showed that both CVVH and CVVHD efficiently removed doripenem with an SC of respectively 67% and 76%.[34] We demonstrated that, despite acceptable *in vivo* concentrations of ertapenem or doripenem after bolus or continuous infusion, a prolonged (4 h) bolus or continuous infusion may be beneficial to keep concentrations longer above MIC. From our study, it can be concluded that imipenem should be replaced by doripenem or meropenem during CRRT. A higher meropenem dose (*i.e.*, 3000 to 6000 mg), may be most adequate whilst preventing resistance of pathogens with MICs between 4 and 8 μg/mL, in particular, *Pseudomonas aeruginosa* strains. Continuous infusion of meropenem preferred mode because the drug is stable for 8 h.[35]

Linezolid

Meyer *et al.* showed that linezolid PK during CVVH was comparable to that of healthy subjects and patients without renal impairment. The t1/2, total clearance and hemofiltration

Table 3A: Pharmacokinetic parameters for all studied antimicrobials

Parameters (mean)	*n*	Dose (mg)	τ (h)	Cmax (μg/mL)	Cmin (μg/mL)	Css (μg/mL)	AUC0- τ (μg.h/mL)	Vd (L)	T1/2 elimination (h)
Ertapenem HD	5	1000	24	17.28	5.75	-	181.90	35	4.41
Ertapenem BD	2	1000	24	32.39	17.86	-	327.23	30	6.79
Imipenem HD Intermittent infusion	4	500	6	13.00	2.10	-	144.88	25.60	1.29
Imipenem BD Intermittent infusion	4	500	6	15.30	3.35	-	209.88	20.70	1.51
Imipenem HD Continuous infusion	2	2000	24	1.43 (D*)	0.78 (D*)	2.74	-	-	-
Imipenem BD Continuous infusion	5	2000	24	4.96 (D*)	2.33 (D*)	7.19	-	-	-
Doripenem HD	3	500	8	10.16	4.29	-	65.56	33.67	2.59
Doripenem BD	7	500	8	12.82	5.62	-	80.98	52.61	4.21
Ceftriaxone HD	2	2000	24	225.62	5.16	-	235.32	51.32	4.19
Ceftriaxone BD	4	2000	24	283.65	6.85	-	415.37	40.13	5.76
Piperacillin HD Intermittent infusion	5	4000	6	145.62	35.56	-	122.52	38.29	3.61
Piperacillin BD Intermittent infusion	2	4000	6	78.35	39.82	-	147.63	50.99	3.99
Piperacillin HD Continuous infusion	10	16000	24	91.62 (D*)	66.38 (D*)	158.71	90.47	-	-
Piperacillin BD Continuous infusion	9	16000	24	147.04 (D*)	109.76 (D*)	256.54	42.74	-	-
Ofloxacin HD	14	200	12	8.47	3.38	-	64.73	32.54	6.58
Ofloxacin BD	8	200	12	8.77	2.44	-	52.02	51.46	8.72
Linezolid HD	2	600	12	17.55	6.68	-	129.63	46.76	6.33
Linezolid BD	3	600	12	21.50	4.30	-	131.31	30.70	4.59
Daptomycin HD	4	6 mg/kg	24	55.22	7.53	-	477.72	20.26	8.53
Daptomycin BD	7	6 mg/kg	24	54.93	10.91	-	510.99	17.70	11.94
Metronidazole HD	12	500	8	15.97	10.61	-	262.57	42	8.22
Metronidazole BD	12	500	8	18.63	10.72	-	236.17	54	10.18
Fluconazole HD	2	400	12	17.40	9.10	-	114.39	73.38	28.54
Fluconazole BD	1	400	12	14.60	7.60	-	96.44	103.71	33.85
Voriconazole BD	3	3 mg/kg	12	7.37	4.79	-	55.00	65.55	7.19

$V_d = CL_s/K_{el}$; $K_{el} = Ln2/T_{1/2Kel}$; $T_{1/2Kel}$ = elimination half-life; D* = loading dose; V_d = volume of distribution; $T_{1/2}$ = elimination half-life; τ = time interval between two administrations; C_{max} = maximum arterial concentration at the end of infusion; C_{min} = trough arterial concentration; C_{ss} = the steady-state arterial concentration for continuous infusion; $AUC_{0-\tau}$ = area under the curve for plasma concentrations between 0 and τ; *n* = number of patients.

clearance were 4.3 ± 1.7 h, 9.3 ± 3.5 L/h and 1.9 ± 0.8 L/h, respectively.[36] Pea *et al.* identified significant elimination of linezolid in patients undergoing CVVH. Total clearance was 25% higher and serum trough concentration 50% lower. In 93% of the patients, serum concentrations above MIC were obtained after the administration of a standard dose (600 mg every 12 h) of linezolid. However, the mean *T*% MIC was only 57% of the dosing interval for pathogens with a MIC of 4 mg/L. Thus, 600 mg of linezolid every 8 h may be necessary to assure optimal antibacterial activity.[37]

We suggest that, whenever possible, time-dependent antibiotics should be administered in continuous infusion during CRRT. As the risk of overdosing is limited and to avoid underdosing, higher than currently recommended doses should be prescribed, particularly when the range of therapeutic concentrations is large.[19]

Drugs moderately influenced by CRRT (or when CVVH clearance largely contributes to total body clearance in AKI)

In this category, antibiotic clearance is close to normal clearance in patients without AKI. Standard doses may be sufficient for optimal treatment.

Concentration-dependent killing

Metronidazole

In patients undergoing dialysis, plasma t 1/2 of metronidazole was 6.8 h, which is comparable with healthy subjects. Dialysis clearance of metronidazole was 60 mL/min with 25% drug eliminated at the start of treatment.[38] Kreeft *et al.* found that plasma metronidazole concentrations in patients with renal insufficiency were similar to those in patients with normal renal function. Moreover, renal insufficiency did not affect beta half-life (6.5 h) or plasma clearance (10.1 L/h) of metronidazole.[39] In our study, mean metronidazole SC, CL_{CVVH} and t1/2 ranged from 82.10 to 89.30%, 26.43 to 58.91 mL/min, and 8.22 to 10.18 h respectively. Accordingly, a dose of 1500 mg once daily is proposed. The currently prescribed dose of 500 mg three times daily should be abandoned!

Ofloxacin

During CVVH, Fuhrmann *et al.* found a mean serum ofloxacin concentration peak of 5.5 ± 0.7 mg/L and a t1/2, hemofiltration clearance, and total removal of 2.8 ± 0.5 h, 89.9 ± 4.5 mL/min, and 76.9% ± 7.1%, respectively.[40] In our study, mean ofloxacin SC, CL_{CVVH} and t1/2 ranged from 59.50 to 66.00%; 18.74 to 52.19 mL/min and 6.58 to

Table 3B: IVOIRE mean pharmacokinetic parameters during CVVH

Paramètres (moyenne)	CLs (mL/min)	Cs (%)	QUF (mL/min)	Dilution factor (%)	CLCVVH (mL/min)	CLCVVH/ CLs (%)	CLNR (mL/min)
Ertapenem HD	91.63	55.90	95.83	77	41.50	45	50.13
Ertapenem BD	50.93	38.70	42.67	84	13.93	27	37
Imipenem HD Intermittent infusion	230.08	66.90	75.83	80	40.58	18	189.50
Imipenem BD Intermittent infusion	158.82	71.60	32.50	86	20.01	13	138.80
Imipenem HD Continuous infusion	506.83	80.70	105.00	77	65.25	13	441.58
Imipenem BD Continuous infusion	193.16	52.40	37.00	86	16.67	9	176.49
Doripenem HD	150.38	90.1	102.00	84	77.20	51	73.18
Doripenem BD	144.33	75.60	32.00	80	19.35	13	124.98
Ceftriaxone HD	141.65	49.60	86.58	88	37.79	27	103.86
Ceftriaxone BD	80.25	64.60	35.24	79	17.98	22	62.27
Pipéracillin HD Intermittent infusion	122.52	96.70	103.05	88	87.69	72	34.83
Pipéracillin BD Intermittent infusion	147.63	92.56	35.50	82	29.94	18	117.69
Pipéracillin HD Continuous infusion	90.48	70.50	98.50	86	59.72	66	30.76
Pipéracillin BD Continuous infusion	42.74	80.10	30.00	80	19.22	45	23.52
Ofloxacin HD	56.93	59.50	102.00	86	52.19	92	49.44
Ofloxacin BD	68.18	66.00	35.50	80	18.74	28	4.74
Linezolid HD	84.94	76.20	102.00	77	59.84	70.50	55.48
Linezolid BD	77.26	80.50	33.00	82	21.78	28	25.10
Daptomycin HD	27.42	12.50	105.00	88	11.55	42	15.87
Daptomycin BD	17.11	15.80	37.00	85	4.97	29	12.14
Metronidazole HD	59.09	82.10	92.00	78	58.91	100	19.78
Metronidazole BD	61.22	89.30	37.00	80	26.43	43	0.18
Fluconazole HD	29.35	59.20	85.00	80	26.05	89	14.79
Fluconazole BD	34.57	75.40	32.00	82	19.78	57	0.30
Voriconazole BD	105.31	40.50	35.00	88	12.47	12	92.84

$CL_{CVVH} = C_s \times Q_{UF}$ x dilution factor = convection clearance; dilution factor = $Q_{blood}/(Q_{blood} + Q_{inf})$; Q_{inf} is the infusion rate of the substitution fluid; CL_S = total body clearance; C_S = Sieving coefficient = 2 x CUF / (Cpre + Cpost); CUF = the drug concentration in ultrafiltrate; Cpre = the drug concentration in prefilter serum corrected for predilution; Cpost = the drug concentration in postfilter serum; *n* = number of patients; CL_{NR} = non renal clearance = CLS - CLCVVH.

Table 4: PK/PD parameters for all studied antibiotics

Antibiotic	Isolated Pathogen	MIC (µg/mL)	T% > MIC	IQ = Cmax/CMI or Css/CMI
Imipenem	*Pseudomonas aeruginosa* (1)	3	34	4
	Escherichia coli (1)	1	57	11
	Enterococcus faecalis (1)	3	37	4
	Streptococcus sp. (1)	2	57	9
	Klebsiella pneumoniae (1)	0.5	85	23
	Pseudomonas aeruginosa (2)	1	43	13
	Enterobacter cloacae (1)	2	65	6
Ofloxacin	*Klebsiella oxytoca* (1)	0.3	-	17
	Moraxella catarrhalis (1)	0,25	-	22
	Enterobacter cloacae(2)	0,25	-	46
	Moraxella catarrhalis (2)	0.3	-	36
	Pseudomonas aeruginosa (3)	2	-	5
	Escherichia coli (3)	1	-	6
	Serratia sp.	1	-	6
Piperacillin	*Enterobacter cloacae* (3)	3	100	11
	Stenotrophomonas maltophila	12.5	84	10
	Streptococcus sp. (2)	0,05	100	700
	Escherichia coli (4)	1	100	49
	Acinetobacter baumanii (1)	9	100	4
	Enterobacter cloacae (4)	3	100	11
	Klebsiella oxytoca (2)	14	100	9
	Pseudomonas aeruginosa (4)	2	100	20
	Escherichia coli (5)	26	58	5
	Proteus mirabilis	0,06	100	583
	Acinetobacter baumanii (2)	4	80	9
	Escherichia coli (6)	0.2	100	159
	Streptococcus haemolysis	0,05	65	10
	Enterobacter aerogenes (1)	1	100	49
Ceftriaxone	*Escherichia coli* (7)	0,02	100	10000
	Enterococcus faecalis (4)	6	48	35
	Escherichia coli (8)	0,02	83	10000
	Enterococcus faecalis (5)	0.3	58	588
Ertapenem	*Klebsiella oxytoca* (3)	0,2	100	50
	Enterobacter cloacae (5)	0,1	100	100
	Escherichia coli (9)	0.5	80	200
	Enterobacter cloacae (6)	1	90	100
	Klebsiella oxytoca (4)	0.5	90	200
	Enterobacter cloacae (7)	1	78	100
	Klebsiella oxytoca (5)	0,06	100	1667
Linezolid	*Staphylococcus aureus* (1)	2.50	32	8
	Staphylococcus aureus (2)	1	90	20
	Staphylococcus aureus (3)	0.5	80	40
Doripenem	*Enterobacter cloacae* (8)	1		12
	Enterobacter aerogenes (2)	0,03	100	375
	Acinetobacter baumanii (3)	2	88	6
	Pseudomonas aeruginosa (5)	1	100	12
	Pseudomonas aeruginosa (6)	2	100	6
	Pseudomonas aeruginosa (7)	1	100	12
	Enterococcus faecalis (6)	1.5	80	9
Daptomycin	*Staphylococcus aureus* (4)	0.5	100	110
	Staphylococcus aureus (5)	1	90	55
	Enterococcus faecalis (2)	1	88	55
	Enterococcus faecalis (3)	1	70	55
Metronidazole	*Bacterioides fragilis* (1)	0.5	90	20
	Bacterioides fragilis (2)	0.5	90	20

Table 5: Dose recommendations for some frequently used antimicrobials during CRRT (CVVH, 25 mL/kg/h)

Antimicrobial	Loading dose	Maintenance dose
Amikacin	30-35 mg/kg	TDM
Meropenem	2 g	2 g over 3 h tid
Piperacillin-tazobactam	4 g/0.5 g	16 g/2 g (CI)
Vancomycin	35 mg/kg over 4 h	30 mg/kg (TDM = 25–30 mg/L)
Teicoplanin	15 mg/kg bid	600 mg od
Linezolid		600 mg tid
Ciprofloxacin	800 mg	400 mg tid
Tigecyclin	150 mg	100 mg bid
Colistin	9 MIU	4.5 MIU tid
Voriconazole	8 mg/kg bid	6 mg/kg bid
Fluconazole		600 mg bid
Cefepime		2 g tid
Gentamycin		7 mg/kg od
Bactrim	1200 mg/240 mg (3 amp)	800 mg/160 mg (2 amp) tid
Clindamycin		900 mg qid

TDM = therapeutic drug monitoring; od = once daily; bid = twice daily; tid = three times daily; qid = four times daily; amp = ampules; CI = continuous infusion; MIU = million units. According to references No. 68-77 – Adapted and changed from reference No. 63.

8.72 h, respectively. However, due to the high volume of distribution, serum concentration is comparable between the standard and high volume group, implying that no dose adaptation is required at increasing CVVH dose. Choi *et al.* [41] studied levofloxacin in an *in vitro* CVVH model and found significantly less drug adsorption on a polyamide than on a polyacrylonitrile (PAN) filter**.** Polyethersulfone used in our study has a pretty bad record regarding almost no drug adsorption.[42] Post-dilution resulted in a small but statistically significant decrease in SC when a PAN filter was used.

Time-dependent killing

Fluconazole

Fluconazole has a low protein binding and a low molecular weight. About 80% is eliminated unchanged by the kidneys. Fluconazole is effectively cleared by hemodialysis and hemofiltration.[43–44] Pittrow and Penk showed that patients undergoing CRRT require a similar loading dose of fluconazole as patients with normal renal function. Thereafter, a maintenance dose is given adjusted for anuria by multiplying with a factor accounting for extracorporeal elimination of the absorbed dose.[45] Yagasaki *et al.* found that continuous hemodiafiltration is highly effective for fluconazole removal. Fluconazole should be administered at a dose of 500 to 600 mg every 12 h [46] but close hepatic, neurological, and ECG (QT interval!) monitoring is mandatory. Bergner *et al.* measured plasma fluconazole concentrations during CVVHDF.[46] All patients reached levels between 16 and 32 mg/L, which remained in this range for minimal 1 and up to 24 h (on average 9.6 h at an UF rate of 2000 mL/h and 15.7 h at an UF rate of 1000 mL/h). Thus, a once-daily dose of 800 mg fluconazole is necessary to achieve optimal fungicidal activity.[47] CVVH effectively removes fluconazole from the circulation by a clearance into the hemofiltrate of approximately 21 mL/min. This implies no dose reduction during CVVH.[48] Muhl *et al.* compared the elimination of fluconazole during continuous veno-venous hemodialysis (CVVHD) and CVVH at different dosages. Extracorporeal clearance (CVVHD 30.5 mL/min, CVVH 17.5 mL/min) and total clearance of fluconazole (CVVHD 37.9 mL/min, CVVH 25.3 mL/min) were significantly higher during CVVHD. During CVVHD, the sieving coefficient (S) (CVVHD) was 0.88 and t1/2 was 14.8–35.1 h. During CVVH, the S(CVVH) was 0.96 and t1/2 was 24.0–51.6 h. Since CVVHD clearance may considerably exceed the clearance in patients with normal renal function, a daily dose of 400 to 800 mg is recommended during CVVHD.[49] In our study, mean fluconazole SC, CL_{CVVH} and t1/2 ranged from 59.20 to 75.40%, 19.78 to 26.05 mL/min, and 28.54 to 33.85 h, respectively. Taken together, fluconazole should be administered at a dose of 500 to 600 mg every 12 h.[46] Point of care dosing of fluconazole could be an interesting option.[50]

Drugs not influenced by CRRT

Time dependent killing

Ceftriaxone

Ceftriaxone clearance in patients receiving CVVHD is equivalent to clearance in subjects with normal renal function. Therefore, no dose adjustment is necessary.[51,52] In hemodialyzed patients, administration of 2 g ceftriaxone resulted in a T > MIC of 88.5 (78.8–98.3) h and 17.7 (13.3–22.0) h for MIC breakpoints of 1 and 8 mg/L, respectively.[53] See comment in PubMed Commons belowIn patients with various degrees of renal impairment, Patel *et al.* confirmed the PK efficacy of a 2 g ceftriaxone dose. T1/2 (group mean ranged from 11.7 to 17.3 h) and plasma clearance (group mean ranged from 529 to 705 ml/h) showed no correlation with creatinine clearance.[54] In our study,

mean ceftriaxone SC, CL_{CVVH} and t1/2 ranged from 49.60 to 64.60%, 17.98 to 37.79 mL/min and 4.19 to 5.76 h, respectively.

Concentration dependent killing

Daptomycin

Salama *et al.* obtained sufficient pre-hemodialysis serum concentrations after thrice-weekly post-hemodialysis administration of 6 mg/kg daptomycin even after a 68 h interval between dialysis sessions.[55] Mean urea and daptomycin reduction ratios were 79.6 ± 5.8% and 57.6 ± 9.2%, respectively. Daptomycin half-life was 19.4 ± 6.5 and 3.8 ± 1.1 h "off" and "on" hemodialysis, respectively, with minimal rebound 1 h post-hemodialysis. Churchwell *et al.* studied transmembrane clearance of daptomycin during CVVH and CVVHD in an *in vitro* model that employed AN69 and polysulfone hemodiafilters at varying ultrafiltrate and dialysate flow rates. Clearance depended on filter type and dialysate and ultrafiltration rates. High ultrafiltrate or dialysate rates resulted in substantial daptomycin clearance.[56] Corti *et al.* found no significant accumulation of daptomycin when a dose of 6 mg/kg was given to patients undergoing CRRT with an effluent flow rate > 30 mL/kg/h.[57] In our study, mean daptomycin SC, CL_{CVVH} and t1/2 ranged from 12.50 to 15.80%, 4.97 to 11.55 mL/min and 8.53 to 11.94 h, respectively.

Voriconazole

Being poorly water-soluble, the intravenous voriconazole formulation includes the vehicle sulfobutylether-beta-cyclodextrin sodium (SBECD). SBECD is not protein-bound and predominantly eliminated by glomerular filtration. Intravenous voriconazole is not recommended in patients with a creatinine clearance < 50 mL/min because of potentially toxic accumulation of SBECD.[58] Tyree *et al.* recently showed that CVVH effectively removed SBECD at a rate similar to the ultrafiltration rate.[59] Voriconazole clearance by CVVH was not clinically significant. Standard doses of intravenous voriconazole can be used safely in patients undergoing CVVH. Quintard *et al.* studied voriconazole PK during HV-CVVH. See comment in PubMed Commons belowThe total body clearance of voriconazole was 5.4 L/h with a half-life of 16.5 h and a distribution volume of 128.6 L. The estimated SC was 0.58 and the filtration clearance 1.39 L/h. HV-CVVH may affect voriconazole disposition more than other techniques.[60,61] When voriconazole doses mount to 6 mg/kg per 12 h, intermittent hemodialysis may fail to completely eliminate SBECD. CRRT is then recommended to avoid vehicle-induced toxicity.[61,62]

STUDY LIMITATIONS

The current study has major flaws and limitations. First, therapeutic drug monitoring remained observational and was not applied to improve PK/PD of the studied antimicrobials. Evaluating the impact of many relevant patient- and technique-related variables influencing PK/PD (*i.e.*, distribution volume, membrane type, MIC of the micro-organisms, quality of resuscitation)[63–65] also remained beyond the scope of the study. Second, at the time of study, all patients received unfractionated heparin for extracorporeal circuit anticoagulation. Today, regional citrate anticoagulation is increasingly used. Citrate better preserves porosity and adsorptive capacity of the membrane, which inherently results in different antimicrobial elimination.[64,66] Third, non-adsorptive membranes were used, which have been progressively supplanted by highly adsorptive membranes. The latter more effectively eliminate antimicrobials through bulk rather than surface adsorption.[64,67,68] Finally, data were gathered during HV-CVVH, which did not prove to be superior to SV-CVVH.[11]

CONCLUSIONS & PERSPECTIVES

As expected, HV-CVVH eliminated more antibiotics than SV-CVVH. All agents were easily filtered. Mean elimination t1/2 of all agents was significantly shorter during HV-CVVH than during SV-CVVH. CLs, CL_{CVVH}, and CL_{NR} of all agents were significantly higher during HV-CVVH.

Antibiotics that are highly removed by CRRT should be preferentially administered as a continuous infusion. A loading dose of 4 g followed by a continuous infusion of 16 g provides the most optimal PK for piperacillin. Regarding carbapenems, our results argue against the use of imipenem during CRRT. Doripenem or meropenem are better options. A meropenem dose of 3 to 6 g is required to adequately treat pathogens with MICs between 4 to 8 mg/L, especially *Pseudomonas aeruginosa* strains. As meropenem was found to be stable for 8 h, it can be given as a continuous perfusion. In almost all patients, linezolid concentrations above the MIC were obtained after administration of a standard dose (600 mg every 12 h) but optimal antibacterial activity at a MIC of 4 mg/L requires 600 mg linezolid every 8 h.

During CRRT, the "classical" 500 mg three times daily metronidazole dose should be abandoned and replaced by **a** 1500 mg once daily dose. The dose of fluconazole must be increased to 500 to 600 mg every 12 h. When higher doses of voriconazole (up to 6 mg/kg per 12 h) are needed, intermittent hemodialysis should be replaced by CRRT to avoid toxicity induced by the SBECD vehicle.

CRRT significantly influences the PK/PD behavior of most antimicrobial agents. This is insufficiently anticipated by the current dosing guidelines. Patients are particularly at

risk for underdosing, which may cause treatment failure and enhance resistance. Table 5 depicts dose recommendations for some major antibiotic and antifungal drugs during CVVH (at a dose of 25 mL/kg/h) that are based upon relevant literature data [69–77] and our own findings.

Conflict of Interest

The authors declare to have no competing interests.

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